REMARKS

Status of the Claims

Claims 1, 17, 19, 20, 35, 42, 47, 78, 93 and 106-127 were pending in the subject application, of which claims 93, 106-112, and 115-127 were examined. Claims 1, 17, 19, 35, 42, 47, 78, 113, and 114 are withdrawn. Claims 19, 20, and 35 are canceled herewith. No new matter is added.

Withdrawn Rejections

Applicants thank the Examiner for the indication that the objection to the Specification is withdrawn and for the indication that the previous rejection of claims 93, 106-112 under 35 U.S.C. 112, and the previous rejection of claims 93, 106, and 107 under 35 U.S.C. 102 have been withdrawn.

Rejection under 35 U.S.C. 102

Claims 93, 106-112, 115-121, and 124-127 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Attie et al. WO 02/22886, hereinafter "Attie". Applicants respectfully request reconsideration.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. The identical invention must be shown in as complete detail as is contained in the claim. Applicants submit that Attie does not describe each element of the invention as set forth in any of claims 93, 106-112, 115-121, or 124-127. For example, Attie does not teach a method of identifying an agent that regulates expression of OXPHOS-CR genes comprising contacting cells with an agent and then determining whether expression of at least two OXPHOS-CR gene products shows a coordinate increase in cells that have been contacted with the agent as compared with an appropriate control, wherein a coordinate increase in the expression of the OXPHOS-CR gene products indicates that the agent regulates the expression of OXPHOS-CR genes, as set forth in claim 93. Tables 1 and 2 of Attie list genes for which Attie detected decreased or increased gene expression, respectively, in adipose tissue of mouse strains with increasing obesity. Table 3 lists changes in gene expression in mouse adipose tissue that correlated with development of hyperglycemia. Attie suggested that one could use the

information disclosed therein to design techniques for intervention in the progression of diabetes and states, "It is possible to up-regulate genes in mammals by adding additional copies of the gene to cells by gene therapy or by triggering up-regulation of genes by introducing known inducing substances into the individual." (p. 27, paragraph [0027]). Applicants submit that these teachings do not describe the method of claim 93, at least for the reason that they fail to describe contacting cells with an agent and then determining whether expression of at least two OXPHOS-CR gene products shows a coordinate increase in cells that have been contacted with the agent as compared with an appropriate control. A step of assessing expression of any genes, let alone OXPHOS-CR genes, in cells that have been contacted with an agent is not taught by Attie. Even if Attie did teach such a step, there is no recognition in Attie that a coordinate increase in the expression of the OXPHOS-CR gene products would indicate that the agent regulates the expression of OXPHOS-CR genes, as recited in claim 93.

Attie also fails to describe elements present in claims that depend on claim 93. For example, Attie does not teach that OXPHOS-CR genes are coordinately regulated and is silent regarding the existence, identification, or use of agents that cause a coordinate increase in the expression of at least two OXPHOS-CR gene products when contacted with a test cell. Thus Attie does not and could not describe that an agent that causes a coordinate increase in the expression of at least two OXPHOS-CR gene products when contacted with a test cell is (i) a potential enhancer of the expression or activity of Errα or Gabp (claim 106); (ii) a potential agent for enhancing mitochondrial biogenesis, expression of Nuclear Respiratory Factor 1 (NRF-1), β-oxidation of fatty acids, total mitochondrial respiration, uncoupled respiration, mitochondrial DNA replication, expression of mitochondrial enzymes, or skeletal muscle fiber-type switching; (claim 107); (iii) a potential agent for the treatment of a disorder (e.g., diabetes) that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function (claims 109 and 124); (iv) a potential agent for increasing expression or activity of Errα or Gabp (claim 110). Attie also does not describe an agent that is a small molecule (claims 108 and 121) or a method comprising contacting a test cell with an agent in vitro (claim 115) or that an agent that increases expression or activity of Errα or Gabp is a potential agent for the treatment of a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function (claims 111 and 125). Attie's statement in paragraph [0021] ("Changes in gene expression in adipose tissue might or might not be sufficient to cause diabetes. Alterations in muscle, liver, and pancreatic b-cells are

probably also required.") does not teach that other tissues "should be studied" as the Examiner contends. It merely comments that gene expression changes in such tissues are probably required to cause diabetes and does not describe determining whether skeletal muscle cells contacted with an agent exhibit a coordinate increase in expression of at least two OXPHOS-CR genes (claim 119). Since Attie does not describe measuring expression of any genes after contacting an agent with a cell, Attie could not and does not teach determining whether an agent regulates expression of genes that are not OXPHOS-CR genes (claim 126).

In summary, Applicants respectfully submit that, for at least the reasons set forth above, Attie clearly does not anticipate any of claims 93, 106-112, 115-121, or 124-127. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. 103

Claims 93, 118, and 122-123 are rejected under 35 U.S.C.103(a) as being allegedly unpatentable over Attie and Scherf et al. 2000, Nature Genetics, 24:236-244 ("Scherf"). Applicants respectfully traverse the rejection.

The Examiner asserts that Scherf provides guidance that artisans were actively using microarrays to identify genes in various cell types that are affected in a disease state and are subsequently affected in the presence of a compound. Applicants respectfully disagree that Scherf provides such guidance. First, although Scherf used microarrays to obtain gene expression profiles from different cancer cell lines, it does not appear that Scherf identified genes that are affected in cancer as compared with the non-diseased state. Scherf assessed gene expression profiles in cell lines derived from cancers of colorectal, renal, ovarian, breast, prostate, lung and central nervous system origin, as well as leukaemias and melanomas (p. 236, last sentence in left column), but does not appear to have assessed gene expression profiles in corresponding normal cells. Second, although Scherf assessed gene expression profiles in cancer cells in the presence or absence of various compounds, Scherf does not appear to have determined whether any of the genes that were affected in the presence of a compound are among the genes whose expression is affected in cancer. (As noted above, Scherf did not specifically identify genes whose expression is affected in cancer). Thus, Scherf neither identified genes that are affected in a disease state nor determined whether genes affected in a disease state are subsequently affected in the presence of a compound. If the Examiner continues to maintain that Scherf provides guidance that artisans were actively using

microarrays to identify genes in various cell types that are affected in a disease state and are subsequently affected in the presence of a compound, Applicants respectfully request that the Examiner indicate specifically where such guidance is found in Scherf.

Furthermore, even if Scherf taught using microarrays to identify genes in various cell types that are affected in a disease state and are subsequently affected in the presence of a compound, which it does not, this would not teach identifying compounds that coordinately affect the expression of multiple genes whose expression is affected in a disease state.

Applicants further submit that even if Attie and/or Scherf taught using microarrays to identify genes in various cell types that are affected in a disease state and are subsequently affected in the presence of a compound, which they do not, it would not be obvious to screen different chemical compounds on various tissues (or cell types) from diabetic patients in order to upregulate SDHB and CYC1. Attie does not describe that one could intervene in the progression of diabetes by upregulating SDHB and CYC1, as the Examiner seems to suggest. Attie states, "Many genes are shown here to be either up-regulated or down-regulated in adipose cells *as an individual first becomes insulin resistant and then diabetic*. Given the techniques of gene therapy now available to use this information to design intervention strategies to counteract that gene expression pattern. The idea is that one would up-regulate genes which would otherwise be in the process of down-regulation and down-regulate genes which were overexpressing" (p.27, paragraph [0027] emphasis added). Attie does not describe the concept of intervening in the expression of any particular subset of the upregulated and/or downregulated genes. Even if Attie did describe this concept, one of ordinary skill in the art would recognize the difficulty, if not futility, of seeking an agent to simultaneously affect multiple independent upregulated and downregulated genes. There is nothing in Attie that would direct the skilled artisan to attempt to identify an agent that would affect both SDHB and CYC1, and certainly nothing that would give the skilled artisan any reasonable expectation of doing so. Indeed, Applicants submit it is unlikely that those genes would be selected based on Attie's teachings. There is no data in Attie showing downregulation of either gene in insulin resistance. Attie did not identify either gene as downregulated in diabetes. Even if there were some teaching in Attie that would point the skilled artisan towards SDHB and/or CYC1, which there is not, Applicants submit that there is no teaching or suggestion in Attie or Scherf, either alone or in combination, of the identification, existence, or use of a substance that causes a coordinate

increase in the expression of any genes whose expression is downregulated in a disease state, and there is certainly no teaching or suggestion of the identification, existence, or use of a substance that causes a coordinate increase in expression of SDHB and CYC1 genes, nor any expectation of doing so. The recognition that OXPHOS-CR genes, such as SDHB and CYC1, are coordinately regulated is found in the instant specification and not in either Attie or Scherf.

In summary, Applicants respectfully submit that Attie and Scherf do not teach all the component parts of the claimed invention and do not render the claimed invention obvious. Withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicant respectfully requests entry of the amendment and consideration of the above remarks. In view of the above amendments and remarks, it is believed that all claims are allowable, and a notice to that effect is respectfully requested. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (617) 951-7000. A petition for a three-(3)-month extension of time is enclosed. Please charge any additional fees to our Deposit Account No. 18-1945, under Order No. WIBL-P01-013 from which the undersigned is authorized to draw.

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Respectfully submitted,

By__/David P. Halstead/_____
David P. Halstead, J.D., Ph.D.
Registration No.: 44,735

Customer Number: 28120

ROPES & GRAY LLP
One International Place
Boston, Massachusetts 02110-2624
(617) 854-2697
(617) 951-7050(Fax)
Attorneys/Agents For Applicant